ELSEVIER

Archives of Medical Research 38 (2007) 265–267

Archives of Medical Research

BRIEF REPORT

Tropospheric Ozone Toxicity vs. Usefulness of Ozone Therapy

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Received for publication July 21, 2006; accepted September 8, 2006 (ARCMED-D-06-00302).

There is a general consensus that continuous inhalation of air polluted with ozone is detrimental for the lungs and vital organs. Even if the concentration of tropospheric ozone is slightly above the tolerated dose, toxicity ensues owing to the cumulative dose inhaled for months. However, in medicine ozone is used as a real drug and a precise concentration and therapeutic dosage must be calibrated against the antioxidant capacity of blood. As ozone reacts with blood, it generates pharmacological messengers such as H_2O_2 and lipid oxidation products (LOPs). These activate several biochemical pathways in blood cells, which after reinfusion are responsible for therapeutic activities lasting several days. Neither acute nor chronic toxicity has been registered.

Key Words: Ozone therapy, Antioxidants, Oxidative stress, Heme-oxygenase-1, Ozone tolerance.

Introduction

There is no doubt that prolonged tropospheric ozone exposure by inhalation damages the respiratory system and extrapulmonary organs. Ozone, by reacting with the vast expanse of the bronchioalveolar space minimally protected by natural antioxidant defenses, induces a huge formation of proinflammatory cytokines, reactive oxygen species (ROS) and toxic lipid oxidation products (LOPs), which first initiate and perpetuate a local chronic inflammation and second, after absorption, reach and damage vital organs. The main reason for the toxicity is due to the cumulative ozone dose that, day after day, elicits the formation of noxious products. This fact has established the dogma that ozone is always toxic and its medical application should be proscribed. This dogma has been reinforced by prejudice, pharmaceutical interests and lack of knowledge of the mechanisms of action of ozone. However, ozonetherapy is becoming very useful either on its own or applied in combination with orthodox medicine in a broad range of pathologies, and it appears important to clarify this controversial issue.

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Tropospheric Ozone Toxicity

Almost everyone living in polluted cities knows that ozone, present in the photochemical smog, should not be breathed and that its continuous inhalation damages the respiratory system and extrapulmonary organs. Not only children, asthmatics, smokers and elderly people are at risk, but also 40% of the U.S. population are adversely affected (1). Chronic oxidative stress established by ozone in the lungs causes a steady release of a huge amount of peroxidative products and proinflammatory cytokines which, after overwhelming the antioxidant defenses, enter the circulation and cause chronic inflammation in several organs. This fact has contributed to establish the wrong dogma that ozone is always toxic and its medical use should be proscribed.

Ozone in Medicine

On the other hand, there is evidence that ozone is today the best water disinfectant for preventing epidemics (2). Moreover, when properly used, the therapeutic effects of ozone cannot be ignored any longer and it is deplorable that medical scientists have a prejudice against the judicious use of ozone in medicine. I would like to argue that ozone, in spite of being a very reactive molecule, is not always toxic, as has been supposed. Three decades of clinical experience

0188-4409/07 $–see front matter.
doi: 10.1016/j.arcmed.2006.09.011

have demonstrated that an appropriate ozone dose in contact with blood for a few minutes *ex vivo* activates several biochemical pathways in erythrocytes, leukocytes and platelets without eliciting any acute or chronic toxicity. Moreover, prompt reinfusion of the ozonated blood in the donor elicits further biological effects on the endothelium and other organs. After having determined the usual therapeutic range (10–50 μg/mL or 0.21–1.05 mM/mL of blood), it appears that the potent antioxidant system of blood is quite able to tame the reactivity of a calculated and precise ozone dose. Using these parameters, there is only a small and transitory decrease of the antioxidant capacity of plasma (3), fully reconstituted within 20 min owing to the efficiency of the redox system (4). Extensive data have been reported in reviews (5–7) and in two books (8,9).

Biological Mechanisms of Action of Ozone

At variance with other complementary approaches, we have demonstrated that ozone, 10-fold more soluble than oxygen, reacts immediately with a number of biomolecules (antioxidants and polyunsaturated fatty acids) present in plasma and within a few minutes disappears but generates a calculated amount of hydrogen peroxide (ROS) and LOPs, which by binding or diffusing into blood cells activate well-defined biochemical pathways (5–9). It is now clear that a ''physiological'' ozone dose, acting as a real drug, triggers an acute and precisely calculated oxidative stress able to activate several biological processes leading to therapeutic benefits. In comparison with the high and fairly constant toxic levels generated by lungs exposed to ozone for months, ozone-generated compounds are regarded as physiological messengers informing the organism of a minimal oxidative stress, which is the critical stimulus for inducing the adaptive response. Indeed, the induction of adaptation to oxidative stress (10) or ''oxidative preconditioning'' represents an additional advantage due to the repetition of small ozonated autohemotherapies able to upregulate the synthesis of several antioxidant enzymes (SOD, GSH-Px, GSH-Rd, GSH-Tr and G-6-PD) and of heme-oxygenase-1 (HO-1), which is one of the most protective enzymes (11). Thus, it must be emphasized that a small, acute stress on blood *ex vivo* is quite different from the prolonged oxidative stress due to tropospheric ozone because the former paradoxically upregulates the antioxidant defenses and the latter induces a progressive inflammation and degeneration. The so-called ''major ozonated autohemotherapy'' was invented in Germany (12) and until now millions of treatments have been performed in patients worldwide without any acute or chronic toxicity (13). Briefly, it consists of collecting 100–200 mL of blood (plus an anticoagulant) in an ozone-resistant glass bottle, adding an equivalent gas volume containing ozone at a precise concentration, gently mixing for 5 min and returning the oxygenated-ozonated blood to the donor-patient during the next 15 min. In this way, all the chemical messengers generated by ozone *ex vivo* diffuse into all the organs and elicit the following biological responses: a) improve blood circulation and oxygen delivery to ischemic tissues, b) correct a chronic oxidative stress by upregulating the antioxidant system and induce HO-1, c) stimulate a mild activation of the immune system and d) procure a state of well-being in the majority of patients by activating the neuroendocrine system (9).

Clinical Results

It has been shown that ozonetherapy is very useful in the following diseases: (1) Chronic osteomyelitis, pleural empyema, abscesses with intractable fistulae, infected wounds, bed sores, chronic ulcers and initial gangrene, necrotizing fasciitis, diabetic foot, skin, mouth, vaginal and rectal bacterial and viral infections and burns (6,7,9). Results are due to the disinfectant properties of ozone and to an enhanced healing allowed by an improved oxygenation and metabolism. Topical therapy with ozonated oil in combination with the parenteral autohemotherapy yields exceptional results (14,15). (2) Advanced ischemic diseases (peripheral obstructive arterial disease and heart ischemia). A brief infusion of ozonated blood is more effective and free of side effects than the conventional 6 h infusion of a prostanoid. The enhanced and sustained vasodilation with an improved oxygen delivery is the key to success (16,17). (3) Age-related macular degeneration (atrophic form only). Even a small increase of oxygen delivery at the foveola level, by acting on the photoreceptors and retinal pigment epithelium, is able to improve visual acuity and quality of life of 66% of patients (8,9). It must be noted that orthodox medicine does not offer any viable option except the administration of antioxidants that represents only a minor advantage. (4) Lumbar and cervical hernial discs as well as localized osteoarthrosis can be treated with a direct or intramuscular small injection of gas. Ozonetherapy is becoming one of the most successful mini-invasive approaches for these affections (18). (5) Dentistry, regarding primary root carious lesions, particularly in children. Ozone sterilizes the dental lesion and enhances the remineralization (19).

In conclusion, there is no doubt that during a chronic inflammatory process, an excessive, continuous and localized release of ROS and LOPs can be detrimental but, under physiological conditions, the two well-known gaseous molecules, NO and CO, can operate as crucial activators, thanks to trace concentrations, short exposure time and particular location. Thus, therapeutic small doses of ozone behave like these two gases. On the other hand, it is now clear that an excessive production of NO, CO and possibly ozone (20) can be deleterious and, therefore, toxicity is strictly linked to the concentration. I know that it will be difficult to eliminate skepticism and the dogmatic assumption that ozone is always toxic but regarding this point, the

reader should reflect about glucose levels in blood: at 0.7−1.0 mg/mL, glucose exerts crucial physiological functions but at 0.4 mg/mL cause a hypoglycemic coma while a constant level >1.3 mg/mL with time similarly can become a killer as shown by the current diabetes epidemic. It is hoped that this brief analysis will stimulate discussion and help to clarify that ozone can be toxic but, when properly used, can be medically useful.

Competing Interests

None declared.

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